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(12) # EUROPEAN PATENT SPECIFICATION

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(54) Thieno(2,3-d)pyrimidine derivatives and salts thereof.

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(73) Proprietor: MITSUBISHI CHEMICAL INDUSTRIES LIMITED
5-2, Marunouchi 2-chome Chiyoda-ku
Tokyo 100 (JP)

(72) Inventor: Ninomiya, Kunihiro
4-12-15 Minami-Naruse
Machida-shi Tokyo (JP)
Inventor: Nitta, Issei
4-13-22 Narusedai
Machida-shi Tokyo (JP)
Inventor: Tobe, Akihiro
3 Sakuradai Midori-ku
Yokohama-shi Kanagawa-ken (JP)
Inventor: Egawa, Mitsuo
2-9-4 Naruse
Machida-shi Tokyo (JP)
Inventor: Kikumoto, Ryoji
1521-29 Nogaya-machi
Machida-shi Tokyo (JP)

(74) Representative: Patentanwälte TER MEER - MÜLLER - STEINMEISTER
Mauerkircherstrasse 45
D-8000 München 80 (DE)

Courier Press, Leamington Spa, England.

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Machida-shi Tokyo (JP)
Inventor: Kikumoto, Ryoji
152 1-29 Nogaya-machi
Machida-shi Tokyo (JP)

(74) Representative: Patentanwälte TER MEER - MÜLLER - STEINMEISTER
Mauerkircherstrasse 45
D-8000 München 80 (DE)

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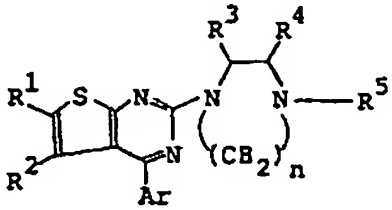
Description

This invention relates to novel thieno[2,3-d]pyrimidine derivatives and salts thereof.

Thienopyrimidine derivatives have been described in EP—A—0 082 023 exhibiting a hypoglycaemic activity, the ability to inhibit aggregation of blood platelets, hypotensive activity and diuretic activity so that they can be used in prophylaxis of thrombosis, hyperglycaemica, hypertension or oedema. The thiopyrimidine residue itself may be substituted by a variety of substituents which do not comprise any aryl substituents.

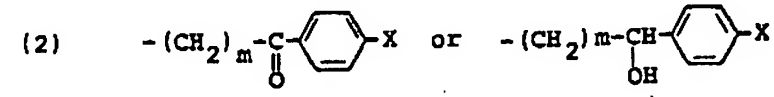
We have done many investigations onto compounds having a psychotropic activity and finally found thieno)2,3-d]pyrimidine derivatives having piperazinyl or homopiperazinyl group on 2-positon and phenyl or thienyl group on 4-position which show such a psychotropic activity. These findings have led us to the present invention.

It is an objection of the invention, therefore, to provide a thieno(2,3-d]pyrimidine derivative represented by the following general formula (I):

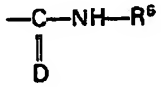


(I)

wherein R^1 and R^2 independently represent hydrogen, halogen (preferably fluorine, chlorine, bromine, iodine end the like), or alkyl group containing t—6 carbon atoms, preferably t—4 carbon atoms, such as methyl, ethyl, propyl or butyl; or alternatively R^1 and R^2 may form a 5- or 6-membered cycloalkylene ring together with two carbon atoms of thienyl group; R^3 and R^4 independently represent hydrogen or alkyl group containing t—6 carbon atoms, preferably t—4 carbon atoms, such as methyl, ethyl, propyl or butyl, R^5 represents (t) hydrogen or alkyl group containing t—6 carbon atoms, preferably t—4 carbon atoms, such as methyl, ethyl, propyl or butyl

(2) 

in which m is an integer of t—3 and X represents halogen such as fluorine, chlorine, bromine, iodine and the like, or

(3) 

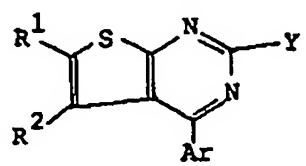
in which R^6 represents alkyl group containing t—6 carbon atoms, preferably t—4 carbon atoms, such as methyl, ethyl, propyl or butyl; Ar represents phenyl which may be substituted or 2- or 3-thenyl group; and n is 2 or 3, and a salt thereof.

When phenyl group represented by Ar is substituted, the substituent may be halogen such as fluorine, chlorine, bromine or iodine; alkyl group containing t—6 carbon atoms such as methyl, ethyl, propyl, butyl or hexyl; alkoxy group containing t—6 carbon atoms such as methoxy, ethoxy, propoxy or butoxy; hydroxyl group; nitro group; amino group; cyano group; or alkyl-substituted amino group such as methylamino, ethylamino, dimethylamino, diethylamino group.

The thieno)2,3-d]pyrimidine derivatives of the invention may be prepared in accordance with any one of the following processes.

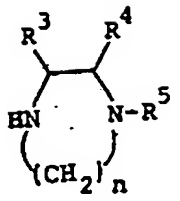
Process (a):

A compound having the general formula (II):

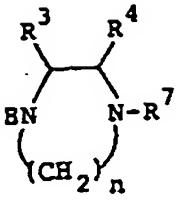


(II)

wherein R^1, R^2 and Ar are as defined above and Y represents halogen, is reacted with an amine represented by the general formula (III) or (IV):



(III)



(IV)

wherein R^3—R^5 and n are as aforementioned defined and R^7 represents a protective group of an amino group. When an amine of the general formula (IV) is used, a deprotection of the group R^7 is required to obtain a compound of the formula (I). The protective groups represented by R^7 are benzyl, formyl, acetyl and benzyloxycarbonyl group.

In the reaction of the pyrimidine derivative of (II) with an amine of (III) or (IV), at leest two equivalents of amine are preferably used since one equivalent of the amine used is utilized for eliminating the hydrogen-halide formed. In order to promote the reaction, the amine (III) or (IV) may often preferably be used in an excess amount up to 20 equivalents.

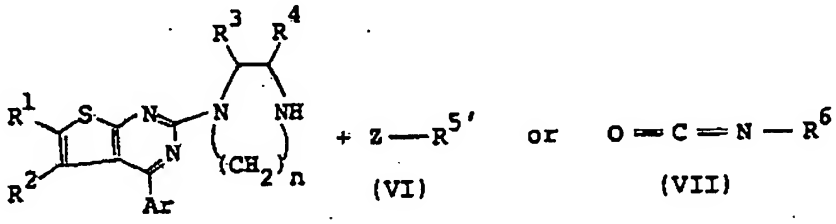
When the reaction is carried out with t equivalent of amine, an acid binding agent such aa a tertiary amine, potassium carbonate and sodium carbonate is added to the reaction mixture. When the rection is carried out with an excess amount of amine, the reaction may proceed with or without a solvent. The solvent which may be used in the reaction is for example inert organic solvents such as alcohols with t—8 carbon atoms, tetrahydrofuran, dioxane, benzene, benzene substituted with alkyl group(s) or halogen(sl, chloroform, dl- or trichloroethylene, acetonitrile, dimethylformemide or dimethylsulfoxide and any mixture thereof. The reaction is generally carried out at a temperature in the range of 20—200°C, preferably in the range of 50—t00°C.

The starting compound, that is, the pyrimidine derivatives represented by the general formula (II) may be prepared according to the method described in Chem. Pharm. Bull., *28*(tt), 3t72(t980).

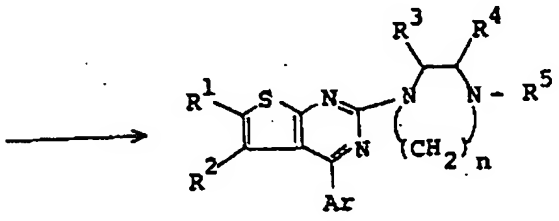
When en amine represented by the general formula (IV) is used in this process, the protective group R^7 for the emino group should be eliminated for obtaining the product (I) in which R^5 is hydrogen after the completion of the reaction. For example, the protective group R^7 of benzyl or benzyloxycarbonyl group can be eliminated by catalytic hydrogenation using palladium carbon es a catalyst. R^7 of formyl or acetyl group can be eliminated by acid hydrolysis.

Process (b):

When a compound of the general formula (I) in which R^6 is not hydrogen may be prepared, a pyrimidine derivative represented by the general formula (V) may be reacted with a compound represented by the general formula (VI) or an alkylisocyanate represented by the general formula (VII) in accordance with the following reaction formula:



(V) (VI) (VII)



(I)

wherein R^1 — R^6, n and Ar are as defined previously, provided that R^5 is not hydrogen, Z represents a halogen atom, $R^{5'}$ is as defined previously in (t) and (2) of R^5, provided that $R^{5'}$ is other than hydrogen atom, and R^6 is as defined previously in (3) or R^5.

The pyrimidine derivative (V) may be a product of the process (a) described above.

The reaction between the pyrimidine derivative (V) and a compound of (VI) can be carried out in a solvent such as acetone, methylethylketone, dimethylformamide or dimethylsulfoxide with the use of

potassium carbonate or sodium carbonate as an acid binding agent.

The reaction of the pyrimidine derivative (V) with an alkylisocyanate (VII) may be carried out at room temperature in a solvent such as dichloromethane or chloroform.

Process (c):

A compound of the general formula (I) obtained by the process (a) or (b) can be subjected to a further reaction to convert the substituent Ar or R^5 to another substituent. Thus, another compound included within the scope of the general formula (I) may be obtained.

For example, a substituent on the group Ar can be converted to another substituent. An example of such a conversion is conversion of nitro group to amino group by iron powder-acetic acid or conversion of bromo group to cyano group by cuprous cyanide in dimethylformamide. An example of the conversion of the group R^5 is conversion of p-fluorophenacyl group to 2-(4-fluorophenyl)-2-hydroxyethyl group by sodium borohydride.

Preferred compounds represented by the general formula (I) which may be prepared by the method (a), (b) or (c) include: 6-methyl-4-phenyl-2-piperazinyl-thieno)2,3-d)pyrimidine; 5,6-dimethyl-4-phenyl-2-piperazinyl-thieno)2,3-d)pyrimidine; 5-methyl-4-phenyl-2-piperazinyl-thieno)2,3-d)pyrimidine; 6-chloro-4-phenyl-2-piperazinyl-thieno(2,3-d)pyrimidine; 4-(2-fluorophenyl)-6-methyl-2-piperazinyl-thieno(2,3-d)-pyrimidine; 4-(2-bromophenyl)-6-methyl-2-piperazinyl-thieno)2,3-d)pyrimidine; 6-methyl-4-(2-methyl-phenyl)-2-piperazinyl-thieno)2,3-d)pyrimidine and 4-(2-cyanophenyl)-6-methyl-2-piperazinyl-thieno)2,3-d)-pyrimidine.

A pharmaceutically acceptable acid addition salt of thieno)2,3-d)pyrimidine derivative represented by the general formula (I) is also included in the scope of the present invention. Such an acid addition salt includes those of an inorganic acid such as hydrochloric acid, phosphoric acid, sulfuric acid and the like, and those of an organic acid such as acetic acid, formic acid, citric acid or p-toluenesulfonic acid.

The thieno(2,3-d)pyrimidine derivatives of the invention have pharmaceutically useful activities, particularly for the central nervous system. Indeed, the compound of the invention has an antagonistic activity against the hypothermal activity of reserpine and an activity for improving the reduction of passive avoidance reaction on an electric shock, which is a model of dysmnesia. Due to such activities, the compounds of the invention are preferably utilized as a pharmeceutical preparation for improvement of intellectual disturbance or depression.

The compound of the invention may be administered solely or in admixture with pharmaceutically acceptable carrier. The composition of a preparation for such use can be varied according to the solubility or chemical properties of the compound or dosage routes or administration plen.

For example, for parenteral administration, such as intramuscular, intravenous or hypodermic injection, the compound of the invention may be made into a sterilized isotonic solution supplemented with other solute such as sodium chloride or glucose. The compound can also be administered orally in the form of a tablet, capsule or granule which contains a suitable vehicle, for example, starch, lactose or sucrose. A cachou, such as troch and lozenge, which may be prepared by mixing the compound of the invention with suger, corn syrup, essence and coloring matter, dehydrating and solidifying, can also be used. Further, the compound can also be administered orally as a solution containing a coloring matter and essence.

A dose of the preparation containing the compound of the invention may be decided by a physician according to the dosage method, the kind of the compound and/or the conditions of a patient to be treated.

Generally, a daily dose of the compound is 0.t—50 mg/kg for parenteral administration, or 0.5—500 mg/kg for oral administration.

The invention will be further illustrated hereinafter by the non-limitative examples.

Example t

Preperation of 6-methyl-4-phenyl-2-piperazinylthieno)2,3-d)pyrimidine by process (A)

Into a solution of 62 g of anhydrous piperazine dissolved with heating in t00 ml of ethanol, t5.64 g of 2-chloro-6-methyl-4-phenyl-thieon)2,3-d)pyrimidine dissolved in 40 ml of warm chloroform is added dropwise under reflux. The mixture is further heated under reflux for an additional hour. Chloroform and ethanol are distilled off under reduced pressure. To the product are added 300 ml of chloroform and 300 ml of water, and then the product is extracted into the chloroform layer. The chloroform layer is washed twice with 200 ml of water and then with saturated aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. The chloroform layer containing the product is concentrated and crystallized from chloroform/cyclohexane. There is obtained t7.t7 g of the product in the form of free base, melting point of t86—t87°C. The product is dissolved in 60 ml of chloroform by heating. To the resultant solution, t.t equivalents of 20% solution of hydrogen chloride in ethanol and then 350 ml of ethanol are successively added. After t00 ml of the solvent is distilled off under reduced pressure end allowed to cool, the deposited crystal is filtered out to obtain t8.20 g of mono hydrochloride salt of the product which has a melting point of 270—280°C (decomposition).

Examples 2—2t

The procedures of Example t are repeated and the compounds shown in Table t are obtained from the corresponding 2-chloro-thieno[2,3-d]pyrimidines and piperazines or homopiperazines.

Table 1:

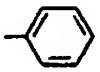
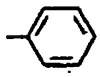
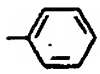
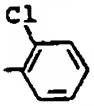
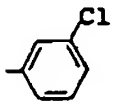
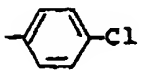
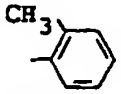
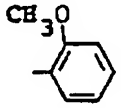
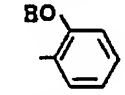
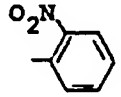
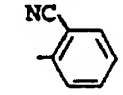
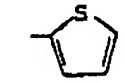
Example No.	R^1	R^2	n	R^4	Ar	Melting Point (°C) Free Base	Mono-hydro-chloride
1	CH_3	H	2	H		186 - 187	270 - 280 (decomp.)
2	H	H	2	H		122 - 123.5	270 - 285 (decomp.)
3	C_2H_5	H	2	H		107 - 110	263 - 268 (decomp.)
4	CH_3	CH_3	2	H		188.5 - 189.5	261 - 280 (decomp.)
5	H	CH_3	2	H		-	266 - 272 (decomp.)
6	H	C_2H_5	2	H		-	263 - 273 (decomp.)
7	Cl	H	2	H		174 - 175	282 - 295 (decomp.)
8	Br	H	2	H		173 - 175	-
9	CH_3	H	3	H		142 - 144	268 - 282 (decomp.)
10	CH_3	H	2	CH_3		138 - 140	270 - 285 (decomp.)
11	CH_3	H	2	H		-	272 - 280 (decomp.)
12	CH_3	H	2	H		134 - 136	267 - 274 (decomp.)
13	CH_3	H	2	H		215 - 217	295 - 310 (decomp.)
14	CH_3	H	2	H		155 - 156	270 - 283 (decomp.)
15	CH_3	H	2	H		-	285 - 295 (decomp.)

Table 1 (cont'd):

Example No.	R^1	R^2	n	R^4	Ar	Melting Point (°C) Free Base	Mono-hydro-chloride
16	CH_3	H	2	H		89 - 91	270 - 283 (decomp.)
17	CH_3	H	2	H		172 - 174	265 - 271 (decomp.)
18	CH_3	H	2	H		194 - 197	288 - 300 (decomp.)
19	CH_3	H	2	H		-	300 - 310 (decomp.)
20	CH_3	H	2	H		150 - 152	289 - 298 (decomp.)
21	CH_3	H	2	H		168 - 169	283 - 295 (decomp.)

Example 22

Preparation of 6-methyl-2-(2-methylpiperazinyl)-4-phenyl-thieno)2,3-d)pyrimidine by process (A): Deprotection of amino group

A mixture of 3 g of 2-chloro-6-methyl-4-phenyl-thieno(2,3-d)pyrimidine, 2.2 g of t-benzyl-3-methylpiperazine, t.t g of sodium carbonate and 4 ml of dimethylformamide is reacted under reflux for 3 hours. After cooling, 80 ml of benzene and 80 ml of water are added and two layers ere separated. The benzene layer is washed twice with t00 ml of water and then with satureted aqueous sodium chloride solution, and dried over anhydrous sodium sulfate. After distilling off benzene, purification of the product by silica gel chromatography using t80 g of silica gel and n-hexane/ethyl acetate (t0:t) as an eluent is carried out. There is obtained 4.3 g of oily 2-(4-benzyl-2-methylpiperazinyl)-6-methyl-4-phenyl-thieno(2,3-d)pyrimidine.

The protected material is dissolved in a mixed solvent of 90 ml of acetic acid and t0 ml of concentrated hydrochloric acid. The resulting solution is subjected to catalytic hydrogenation at 70°C under atmospheric pressure for 4 hours using 0.5 g of palladium black as a catalyst. After filtering out the catalyst, acetic acid and hydrochloric acid are distilled off. t50 ml of ethyl acetate and t00 ml of t0% aqueous solution of potassium carbonate and two leyers are separated. The ethyl acetate layer is washed with water and then with saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. After distilling off ethyl acetate, recrystallization from chloroform/n-hexane gives t.85 g of the desired product with a melting point of t68—t70°C.

Example 23

Preparation of 2-(4-(4-fluorophenacyl)-piperazinyl)-6-methyl-4-phenyl-thieno)2,3-d)pyrimidine by process (B)

In 6 ml of methylethylketone, 2.03 g of 6-methyl-4-phenyl-2-piperazinyl-thieno)2,3-d)pyrimidine, t.25 g of 4-fluorophenacyl chloride and 0.73 g of triethylamine are reacted under reflux for 5 hours. After cooling, 70 ml of chloroform is added to the reaction mixture. The solution is washed twice with t00 ml of water and then saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. After distilling off chloroform, crystallization from diethylether/methanol gives 2.68 g of the product which has a melting point of t4t—t42°C.

Example 24

Preparation of 2-(4-(2-(4-fluorophenyl)-2-hydroxyethyl)-piperazinyl)-6-methyl-4-phenyl-thieno)2,3-d)pyrimidine by process (C): Conversion of R^6

Into a mixture of t0 ml of chloroform and t0 ml of ethanol is dissolved t.34 g of 2-(4-(4-fluorophenacyl)-piperazinyl)-6-methyl-4-phenyl-thieno)2,3-d)pyrimidine, and then 0.23 g of sodium borohydride is added at room temperature. After reaction for one hour, 60 ml of chloroform and t00 ml of water are

added and two layers are separated. The chloroform layer is washed with t00 ml of water and then with saturated aqueous solution of sodium chloride, and dried over anhydrous sodium sulfate. Chloroform is distilled off and t.27 g of the desired crystal is obtained from methanol. The product has a melting point of t80—t8t.5°C.

Example 25

Preparation of 4-(2-aminophenyl)-6-methyl-2-piperazinyl-thieno)2,3-d]pyrimidine by process (C): Conversion of substituent on the group Ar

Into a mixed solvent of 8 ml of ethanol, 3.5 ml of water and 4 ml of acetic acid, t.25 g of 6-methyl-4-(2-nitrophenyl)-2-piperazinyl-thieno(2,3-d)pyrimidine is dissolved, and t.5 g of iron powder is gradually added at 90°C over one hour. After the reaction at 90°C further for 20 minutes, 25 ml of ethanol and 6 ml of water are added. The reaction mixture is filtered by a Celite® layer. The Celite® layer is washed with hot ethanol and the washings and the filtrate are combined and distilled off under reduced pressure. The residue is treated with 20 ml of t0% aqueous solution of sodium carbonate and with 80 ml of chloroform and filtered by a Celite layer. The chloroform layer is separated and dried over anhydrous sodium sulfate. Chloroform is removed to concentrate and crystallization from chloroform/cyclohexane gives the desired product (0.93 g) which has a melting point of 232—236°C.

Example 26

Pharmecological tests

A. Antagonistic activity against reserpine-induced hypothermia

A test was carried out using ddY mele mice of 22—25 g in body weight, one group consisting of 6 mice.

The body temperature of mice was approximately 38°C before the test. At 4 hours after intraperitoneal administretion of reserpine in an amount of 5 mg/kg the body temperature of mice was reduced by approximately 8°C in average. The test compound was simultaneously orally administered with 5 mg/kg of reserpine, and the degree of antagonistic effect of the test compound on the hypothermal action of reserpine was measured. This test has hitherto been the commonest method for evaluating anti-depressant activity.

When the hypothermal activity of reserpine was completely inhibited, the antagonistic activity was evaluated as t00%. Percentage (%) of an antagonistic activity was calculated by varying the doses of each test compound. In addition, a dose exhibiting 50% antagonistic activity, i.e. ED_{50}, of each compound was calculated by Litchfield-Wilcoxon method described in J. Pharmacol. Exp. Ther., 96, 99 (t949).

The activities of 8 compounds of the present invention are shown in Table 2. As a control, the activity of the known anti-depressive agent, amitriptyline, is also shown in Table 2. Further, Table 2 also shows the acute toxicities, LD_{50}, in male mice.

TABLE 2

Compound (Example No.)	ED_{50} (mg/kg, p.o.)	LD_{50} (mg/kg, p.o.)
t	2.0	tt70
4	t.8	t330
5	4.0	275
7	2.4	—
14	0.27	tt t0
t5	2.9	t750
t6	0.5	t400
20	t.5	370
Amitriptyline	t4.5	380

B. Passive avoidance response failure by electric shock as model of amnesia

The method described by Susan J. Sara in Psychopharmacology, 68, 235—24t (t980) was used as an amnesia model.

The test apparatus used, called as "Two Compartment Avoidance Box", consisted of a large lit compartment and a small dark compartment having a grid floor to which an electric current can be applied,

these two compartments being painted bleck innerly end connected to each other.

Male Wistar rats of t70—220 g in body weight enter into the small box soon after they are introduced into the large box. When a rat enters into the small box, the inlet is closed and an electric current of 3 mA for 5 seconds is applied to the grid floor, so that the period for which the same rat does not enter into the small box is markedly prolonged when the rat is again introduced into the large box after 3 hours or more. This response is called as "passive avoidance response".

However, if an electric shock of 60 mA, 200 Hz for 0.8 second is given to the rat by electrodes set on both ears of the rat immediately after the rat comes out of the small box upon the application of the electric current, the "passive avoidance response" is inhibited. Indeed, the period for entering into the small box from the large box, latency, is shortened. This phenomenon is caused by loss of memory of the electric current applied from the grid floor by the electric shock. The shortened time of latency is used as an index of the loss of memory.

A memory improvement effect of e test compound is expressed in the degree of prolongation of latency (% improvement) in a test carried out 3 hours or more after the oral administration of the test compound after application of an electric shock.

The activities of three compounds of the present invention are shown in Table 3. The present compounds have a comparable activities as compared with a known nootropic agent, piracetam.

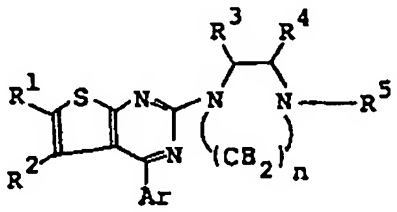
TABLE 3

Compound (Example No.)	Dose (mg/kg, p.o.)	Improvement (%)
t	25	6.8
	t00	22.7
t4	25	30.9
	t00	51.5
t6	25	t2.8
	t00	46.6
Piracetam	250	22.0
	500	t4.t

As is seen from the aforementioned data, the compounds of the invention will be useful for improving various depressive conditions including a psychosomatic disease or manic-depressive insanity, and for improving higher dysfunction of the brain such as amnesia by presenile or senile dementia or encephalopathic sequelae.

Claims

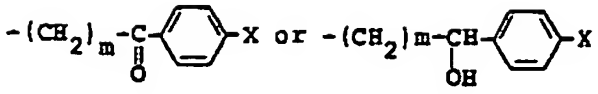
t. A thieno]2,3-d]pyrimidine derivative represented by the general formula (I):



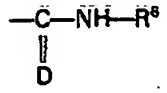
(I)

wherein R^1 and R^2 independently represent hydrogen, halogen or alkyl groups having t to 6 carbon atoms; or R^1 and R^2 may concatenate to form a cycloalkylene group having 5 or 6 ring carbon atoms; R^3 and R^4 independently represent hydrogen or alkyl groups having t to 6 carbon atoms; R^5 represents a member selected from

(t) hydrogen or alkyl having t to 6 carbon atoms.

(2) 

in which m is an integer of from t to 3 and X represents halogen, or

(3) 

in which R^6 represents an alkyl group having t to 6 carbon atoms;

Ar represents phenyl, phenyl substituted by halogen, alkyl groups containing t to 6 carbon atoms, alkoxy groups containing t to 6 carbon atoms hydroxyl, nitro, amino, cyano, alkyl-substituted amino groups or a 2- or 3-thienyl group and n is 2 or 3, and a salt thereof.

2. The derivative according to claim t, characterized in that n is 2.

3. The derivative according to claim 2, characterized in that R^5 is hydrogen.

4. The derivative according to claim 3, characterized in that R^4 is hydrogen.

5. The derivative according to claim 4, characterized in that R^1 is methyl or chloro and R^2 is hydrogen or methyl.

6. The derivative according to claim 5, characterized in that R^1 is methyl and R^2 is hydrogen.

7. The derivative according to claim 5, characterized in that Ar is unsubstituted phenyl or 2-fluorophenyl, 2-bromophenyl, 2-methylphenyl or 2-cyanophenyl group.

8. 6-Methyl-4-phenyl-2-piperazinyl-thieno[2,3-d]pyrimidine.

9. 5,6-Dimethyl-4-phenyl-2-piperazinyl-thieno[2,3-d]pyrimidine.

t0. 5-Methyl-4-phenyl-2-piperazinyl-thieno[2,3-d]pyrimidine.

t1. 6-Chloro-4-phenyl-2-piperazinyl-thieno[2,3-d]pyrimidine.

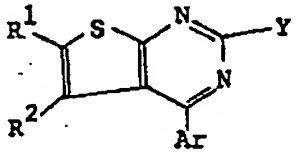
t2. 4-(2-Fluorophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine.

t3. 4-(2-Bromophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine.

t4. 6-Methyl-4-(2-methylphenyl)-2-piperazinyl-thieno[2,3-d]pyrimidine.

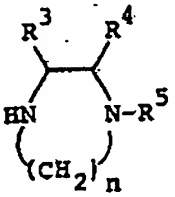
t5. 4-(2-Cyanophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine.

t6. A process for preparing a thieno[2,3-d]pyrimidine derivative according to claim t represented by the general formula (I) characterized in that a compound represented by the general formula (II):

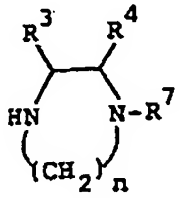


(II)

is reacted with a compound represented by the general formula ((II) or (IV):



(III) ,

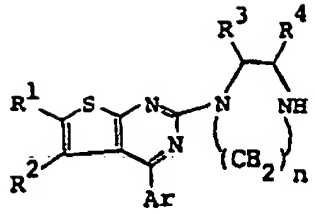


(IV)

wherein R^1 to R^6, Ar and n are as defined above, Y represents halogen and R^7 represents a protective group of amino group; and when the compound of (IV) is used the protective group R^7 is then deprotected.

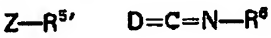
t7. The process according to claim t6, characterized in that the protective group R^7 is selected from benzyl, formyl, acetyl and benzyloxycarbonyl group.

t8. A process for preparing a thieno[2,3-d]pyrimidine derivative according to claim t characterized in that a compound represented by the general formula (V):



(V)

is reacted with a compound represented by the general formula (VI) or (VII):



(VI), (VII)

wherein R^1 to R^4, Ar and n are as defined above, $R^{5'}$ is as defined above for R^5 (1) and (2), and R^6 is as defined above for R^5 (3).

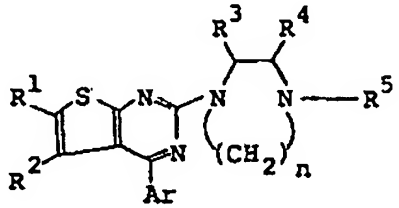
19. A process for preparing a thieno)2,3-d]pyrimidine derivative according to claim 1 represented by the general formula (I) characterized in that a substituent Ar or R^6 of a thieno)2,3-d]pyrimidine derivative according to claim 1 is converted to another substituent of the definition given in claim 1.

20. A pharmaceutical preparation in a dosage unit form, which contains a thieno)2,3-d]pyrimidine derivative according to claim 1 as an active ingredient.

21. A pharmaceutical composition of a thieno(2,3-d]pyrimidine derivative according to claim 1 in association with a pharmaceutically acceptable carrier.

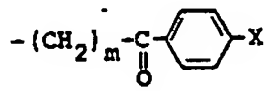
Patentansprüche

1. Thieno)2,3-d]pyrimidin-Derivat der allgemeinen Formel (I):

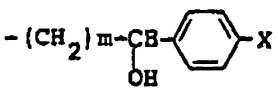


(I)

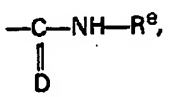
worin R^1 und R^2 voneinander unabhängig Wasserstoffatome, Halogenatome oder Alkylgruppen mit 1 bis 6 Kohlenstoffatomen oder R^1 und R^2 gemeinsam eine Cycloalkylengruppe mit 5 oder 6 Ringkohlenstoffatomen; R^3 und R^4 voneinander unabhängig Wasserstoffatome oder Alkylgruppen mit 1 bis 6 Kohlenstoffatomen, R^5 eine Gruppe ausgewählt aus der
(1) Wasserstoffatome oder Alkylgruppen mit 1 bis 6 Kohlenstoffatomen,
(2) Gruppen der Formel



oder der Formel



worin m eine ganze Zahl von 1 bis 3 und X ein Halogenetom darstellen, und
(3) Gruppen der formel



worin R^6 eine Alkylgruppe mit t bis 6 Kohlenstoffatomen darstellt, umfassenden Gruppe;

Ar eine Phenylgruppe, eine mit Halogen, Alkylgruppen mit t bis 6 Kohlenstoffatomen, Alkoxygruppen mit t bis 6 Kohlenstoffatomen, Hydroxylgruppen, Nitrogruppen, Aminogruppen, Cyanogruppen, alkylsubstituierten Aminogruppen substituierte Phenylgruppe oder eine 2- oder 3-Thienylgruppe und n 2 oder 3 und ein Salz davon bedeuten.

2. Derivat nach Anspruch t, dadurch gekennzeichnet, daß n 2 bedeutet.

3. Derivat nach Anspruch 2, dadurch gekennzeichnet, daß R^5 ein Wasserstoffatom bedeutet.

4. Derivat nach Anspruch 3, dadurch gekennzeichnet, daß R^4 ein Wasserstoffatom bedeutet.

5. Derivat nach Anspruch 4, dadurch gekennzeichnet, daß R^1 eine Methylgruppe oder eine Chloratom und R^2 ein Wasserstoffatom oder eine Methylgruppe bedeuten.

6. Derivat nach Anspruch 5, dadurch gekennzeichnet, daß R^1 eine Methylgruppe und R^2 ein Wasserstoffatom bedeuten.

7. Derivat nach Anspruch 5, dadurch gekennzeichnet, daß Ar eine unsubstituierte Phenylgruppe oder eine 2-Fluorphenyl-, 2-Bromphenyl-, 2-Methylphenyl- oder 2-Cyanophenylgruppe bedeutet.

8. 6-Methyl-4-phenyl-2-piperazinylthieno)2,3-d]pyrimidin.

9. 5,6-Dimethyl-4-phenyl-2-piperazinylthieno)2,3-d]pyrimidin.

t0. 5-Methyl-4-phenyl-2-piperazinylthieno)2,3-d]pyrimidin.

t1. 6-Chlor-4-phenyl-2-piperazinylthieno)2,3-d]pyrimidin.

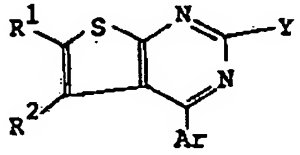
t2. 4-(2-Fluorphenyl)-6-methyl-2-piperazinylthieno(2,3-d]pyrimidin.

t3. 4-(2-Bromphenyl)-6-methyl-2-piperazinylthieno[2,3-d]pyrimidin.

t4. 6-Methyl-4-(2-methylphenyl)-2-piperazinylthieno)2,3-d]pyrimidin.

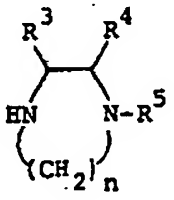
t5. 4-(2-Cyanophenyl)-6-methyl-2-piperazinylthieno)2,3-d]pyrimidin.

t6. Verfahren zur Herstellung eines Thieno)2,3-d]pyrimidin-Derivats nach Anspruch t der allgemeinen formel)I), dadurch gekennzeichnet, daß man eine Verbindung der allgemeinen Formel (II):

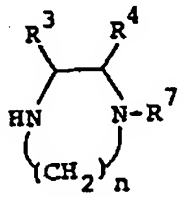


(II)

mit einer Verbindung der allgemeinen Formel (III) oder (IV):



(III)

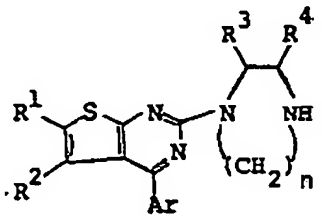


(IV)

worin R^1 bis R^6, Ar und n die obigen Bedeutungen haben,
Y ein Halogenatom und R^7 eine Aminogruppenschutzgruppe bedeuten, umsetzt und bei Verwendung der Verbindung (IV) die Schutzgruppe R^7 dann entfernt.

t7. Verfahren nach Anspruch t6, dadurch gekennzeichnet, daß die Schutzgruppe R^7 aus der Benzyl-, Formyl-, Acetyl- und Benzyloxycarbonylgruppen umfassenden Gruppe gewählt ist.

t8. Verfahren zur Herstellung eines Thieno(2,3-d]pyrimidin-Derivats nach Anspruch t, dadurch gekennzeichnet, daß man eine Verbindung der allgemeinen Formel (V):



(V)

mit einer Verbindung der allgemeinen Formel (VI) oder (VII):

$Z—R^{5'}$ (VI), $D=C=N—R^6$ (VII)

worin R^1 bis R^4, Ar und n die obigen Bedeutungen haben, $R^{5'}$ die Bedeutung von R^5 (t) und (2) und R^6 die Bedeutung von R^6 (3) haben, umsetzt.

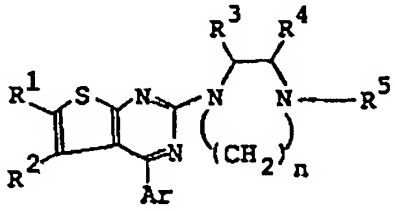
t9. Verfahren zur Herstellung eines Thieno[2,3-d]pyrimidin-Derivats nach Anspruch t der allgemeinen Formel (I), dadurch gekennzeichnet, daß man einen Substituenten Ar oder R^5 des Thieno[2,3-d]pyrimidin-Derivats nach Anspruch t in einen anderen Substituenten der in Anspruch t angegebenen Definition umwandelt.

20. Pharmazeutische Zusammensetzung in Dosiseinheitsform, enthaltend ein Thieno[2,3-d]pyrimidin-Derivat nach Anspruch t als aktiven Bestandteil enthält.

2t. Pharmazeutische Zusammensetzung eines Thieno[2,3-d]pyrimidin-Derivats nach Anspruch t in Verbindung mit einem pharmazeutisch annehmbaren Trägerstoff.

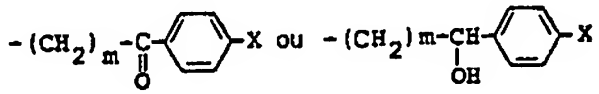
Revendications

t. Dérivé de thiéno [2,3-d] pyrimidine représenté par la formule générale (I):

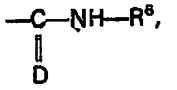


(I)

dans laquelle
— R^1 et R^2 représentent indépendamment hydrogène, halogène ou des groupes alkyle ayant de t à 6 atomes de carbone; ou bien R^1 et R^2 peuvent former, conjointement avec les atomes de carbone qui les portent, un groupe cycloalkylène ayant 5 ou 6 atomes dans le cycle;
— R^3 et R^4 représentent indépendamment hydrogène ou des groupes alkyle ayant de t à 6 atomes de carbone;
— R^5 représente un élément choisi parmi:
(t) hydrogène ou alkyle ayant de t à 6 atomes de carbone;

(2) 

où; m est un nombre entier allant de t à 3; et X représente halogène; ou

(3) 

ou R^6 représente un groupe alkyle ayant de t à 6 atomes de carbone;
—Ar représente phényle, phényle substitué par halogène, des groupes alkyle contenant de t à 6 atomes de carbone, des groupes alcoxy contenant de t à 6 atomes de carbone, hydroxyle, nitro, amino, cyano, des groupes amino substitués par alkyle ou un groupe thiényl-2 ou -3; et
— n vaut 2 ou 3,
ainsi que les sels de ce dérivé.

2. Dérivé selon la revendication t, caractérisé par le fait que n vaut 2.

3. Dérivé selon la revendication 2, caractérisé par le fait que R^5 représente hydrogène.

4. Dérivé selon la revendication 3, caractérisé par le fait que R^4 représente hydrogène.

5. Dérivé selon la revendication 4, caractérisé par le fait que R^1 représente méthyle ou chloro, et R^2 représente hydrogène ou méthyle.

6. Dérivé selon la revendication 5, caractérisé par le fait que R^1 représente méthyle, et R^2 représente hydrogène.

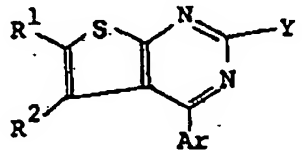
7. Dérivé selon la revendication 5, caractérisé par le fait que Ar représente un groupe phényle non substitué ou un groupe fluoro-2 phényle, bromo-2 phényle, méthyl-2 phényle ou cyano-2 phényle.

8. Méthyl-6 phényl-4 pipérazinyl-2 thiéno [2,3-d] pyrimidine.

9. Diméthyl-5,6 phényl-4 pipérazinyl-2 thiéno (2,3-d) pyrimidine.

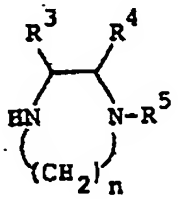
t0. Méthyl-5 phényl-4 pipérazinyl-2 thiéno [2,3-d] pyrimidine.

t1. Chloro-6 phényl-4 pipérazinyl-2 thiéno [2,3-d] pyrimidine.
t2. (Fluoro-2 phényl)-4 méthyl-6 pipérazinyl-2 thiéno [2,3-d] pyrimidine.
t3. (Bromo-2 phényl)-4 méthyl-6 pipérazinyl-2 thiéno [2,3-d] pyrimidine.
t4. Méthyl-6 (méthyl-2 phényl)-4 pipérazinyl-2 thiéno [2,3-d] pyrimidine.
t5. (Cyano-2 phényl)-4 méthyl-6 pipérazinyl-2 thiéno [2,3-d] pyrimidine.
t6. Procédé de préparation d'un dérivé de thiéno [2,3-d] pyrimidine tel que défini à la revendication t, représenté par la formule générale (I), caractérisé par la fait que l'on fait réagir un composé représenté par la formula générale (II):

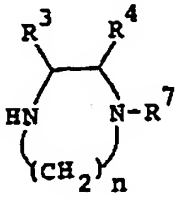


(II)

evec un composé représenté par la formule générale (III) ou (IV):



(III),

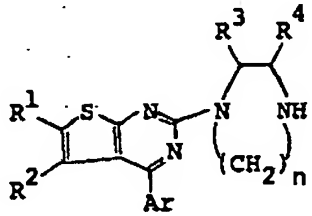


(IV)

dans lequelle:
— R^1 à R^5, Ar et n sont tels que définis ci-dessus;
— Y représente halogène; et
— R^7 représente un groupe protecteur du groupe amino; et, lorsqu'on utilise le composé de formule (IV), le groupe protecteur R^7 est alors éliminé.

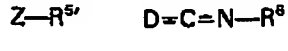
t7. Procédé selon la revendication t6, caractérisé par le fait que le groupe protecteur R^7 est choisi parmi les groupes benzyle, formyle, acétyle et benzyloxycarbonyle.

t8. Procédé de préparation d'un dérivé de thiéno [2,3-d] pyrimidine tel que défini à la revendication t, caractérisé par le fait que l'on fait réagir un composé représenté par la formule générale (V):



(V)

avec un composé représenté par la formule générale (VI) ou (VII):



(VI), (VII).

dans laquelle:
— R^1 à R^4, Ar et n sont tels que définis ci-dessus,
— $R^{5'}$ est tel que défini ci-dessus pour R^5 (t) et (2);
— R^6 est tel que défini ci-dessus pour R^5 (3).

t9. Procédé de préperation d'un dérivé de thiéno [2,3-d] pyrimidine tel que défini à la revendicetion t, représenté par la formule générale (I), caractérisé par le fait que l'on convertit le substituant Ar ou R^5 d'un dérivé de thiéno [2,3-d] pyrimidine tel que défini à la revendicetion t, en un autre substituant de la définition donnée à la revendication t.

20. Préparation pharmaceutique se présentant sous la forme d'une unité de dosage, qui contient un dérivé de thiéno [2,3-d] pyrimidine tel que défini à la revendication t en tant qu'ingrédient actif.

21. Composition pharmaceutique d'un dérivé de thiéno [2,3-d] pyrimidine tel que défini à la revendication t en association avec un support pharmaceutiquement acceptable.